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Prenatal exposure to a natural disaster and early development of psychiatric disorders during the preschool years: Stress in Pregnancy Study

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Abstract

Background.—Growing evidence shows an association between *in-utero* exposure to natural disasters and child behavioral problems, but we still know little about the development of specific psychopathology in preschool-aged children.

Methods.—Preschool children (n=163, mean age=3.19, 85.5% racial and ethnic minorities) and their parents (n=151) were evaluated annually at ages 2–5 to assess the emergence of psychopathology using the Preschool Age Psychopathological Assessment (PAPA), a parent-report structured diagnostic interview developed for preschool-age children. Sixty-six (40.5%) children were exposed to Sandy Storm (SS) in-utero and 97 (59.5%) were not. Survival analysis evaluated patterns of onset and estimated cumulative risks of psychopathology among exposed and unexposed children, in total and by sex. Analyses were controlled for the severity of objective and subjective SS-related stress, concurrent family stress, and demographic and psychosocial

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Fit Statistics for Latent Profiles Extracted by Prenatal Stress Indices.

Table S2. The test of equality on survival distributions by Superstorm Sandy exposure and child sex.

Table S3. Characteristics of participants included and not included in this study.

Conflict of interest statement: See Acknowledgements for full disclosures.

confounders, such as maternal age, race, SES, maternal substance use, and normative prenatal stress.

Results.—Exposure to SS *in-utero* was associated with a substantial increase in depressive disorders (Hazard Ratio (HR)=16.9, p=.030), anxiety disorders (HR=5.1, p<.0001), and attention deficit/disruptive behavioral disorders (HR=3.4, p=.02). Diagnostic rates were elevated for generalized anxiety disorder (GAD) (HR=8.5, p=.004), attention-deficit/hyperactivity disorder (ADHD) (HR=5.5, p=.01), oppositional defiant disorder (ODD) (HR=3.8, p=.05), and separation anxiety disorder (SAD) (HR=3.5, p=.001). Males had distinctively elevated risks for attention deficit/disruptive behavioral disorders (HR=7.8, p=.02), including ADHD, CD, and ODD, whereas females had elevated risks for anxiety disorders (HR=10.0, p<.0001), phobia (HR=2.8, p=.02) and depressive disorders (HR=30.0, p=.03), including SAD, GAD and dysthymia.

Conclusions.—The findings demonstrate that *in-utero* exposure to a major weather-related disaster (SS) was associated with increased risk for psychopathology in children and provided evidence of distinct psychopathological outcomes as a function of sex. More attention is needed to understand specific parent, child and environmental factors which account for this increased risk, and to develop mitigation strategies.

Keywords

Natural disasters; Anxiety; Disruptive behavior; Developmental Psychopathology; Sex differences

Introduction

Climate change is a challenging problem worldwide. In addition to the physical and environmental consequences it produces, climate change poses important threats to the mental health of individuals and our society. The increasing frequency and extreme nature of events such as hurricanes, tropical storms, wildfires, flooding, and drought causes serious disruptions to everyday life, including loss of power, water, transportation, and communication systems (Clemens, von Hirschhausen, & Fegert, 2020; Zakrison, Valdés, & Shultz, 2020). These disruptions affect the most vulnerable the hardest (Zahran, Snodgrass, Peek, & Weiler, 2010) – including pregnant women and their babies *in-utero*. The consequences of this can be life-long because perturbations that occur during the sensitive period of development may elicit structural and functional changes to fetal organs (Barker, 1995), particularly the brain.

The Developmental Origin of Health and Disease (DOHaD) hypothesis postulates that exposure to suboptimal prenatal conditions has a serious, deleterious impact on health throughout the lifespan (Barker, & Osmond, 1986; Roseboom, Van Der Meulen, Ravelli, Osmond, Barker, et al., 2001; Drake, Tang, & Nyirenda, 2007). Early human studies which examined the consequences of suboptimal perinatal conditions, such as low birthweight, demonstrated a 2-to 3-fold increased risk of behavioral problems, including attention problems and impulsivity (Milberger, et al., 1997; Botting, Powls, Cooke, & Marlow, 1997) and anxiety (Breslau, Klein, & Allen, 1988; Hirshfeld-Becker, Biederman, Faraone, Robin, Friedman, et al., 2004). More recent evidence suggests that there may be a sex-related vulnerability for compromised behavioral outcomes following prenatal stress exposure, with

female offspring being more likely than males to have greater internalizing symptoms, anxiety, and depression (Sharp, Hill, Hellier, & Pickles, 2015), greater negative emotionality (Braithwaite, Pickles, Sharp, Glover, O'Donnell, et al., 2017), and heightened cortisol levels when re-exposed to stress (Ping, Laplante, Elgbeili, Hillerer, Brunet, et al.,2015). Some studies have reported a greater decrease in placental 11B-HSD2 (an enzyme that converts active cortisol to the inactive cortisone) following maternal stress in female fetuses compared to males, which leaves female fetuses more vulnerable to maternal stress (Mina, Räikkönen, Riley, Norman, & Reynolds, 2015).

Several studies have examined the proximal impact of natural disasters on child physical and neurobehavioral status, including the Canadian Ice Storm (Laplante, Brunet, & King, 2016); Hurricane Andrew; Hurricane Katrina (Xiong, Harville, Buekens, Mattison, Elkind-Hirsch, et al., 2008); and Superstorm Sandy (SS) (Nomura, Zhang, & Hurd, 2021). Findings demonstrated poorer birth outcomes, including fetal hypoxia, (Zahran et al., 2010), preterm births and lower birthweight (Xiong, et al., 2008), after hurricane exposures. Recent reviews (van den Bergh, et al., 2017, Monk et al., 2019) have highlighted that *in-utero* exposure to stress is associated with suboptimal behavioral outcomes, especially related to stress reactivity, but much less is known about the longitudinal impact of *in-utero* exposure on child psychiatric disorders. Our longitudinal project, the Stress in Pregnancy (SIP) Study, focused on the effects of a unique convergence of stress caused by SS, which made landfall in Metropolitan New York in 2012, for the risk of psychopathology in preschool children. We have previously reported that *in-utero* exposure to SS was associated with greater mental health problems (anxiety, depression, and somatization) at age 2, based on dimensional rating scales. The study found a significant upward trajectory of anxiety among the exposed compared to the unexposed children during ages 2–4 (Nomura et al., 2021). To date, however, there has been no report of diagnostic outcomes ascertained by clinical interviews during the preschool years among this cohort, or any other, in relation to biological sex.

The objective of this study was to assess the impact of exposure to SS *in-utero* on subsequent development of childhood psychopathology using a longitudinal design and categorical diagnostic measures validated for use in the preschool years, and to examine sex-specific effects of this exposure.

Methods

Participants

Preschool children (n=163, mean age=3.19) and their parents (n=151) were selected to participate in this study. Figure 1 shows that 66 children (40.5%) were exposed to SS *in-utero* while the remaining 97 (59.5%) were not, including those born prior to SS (n=56) or conceived after SS (n=41). Mothers agreed to participate in a study examining diagnostic outcomes via structured clinical interview (Egger, Angold, Small, & Copeland, 2019). Interviewers were clinical psychologists with a graduate degree; intensive training, monitoring, and interrater reliability testing were conducted. All participants provided written consent; the protocol was approved by the Institutional Review Boards at the City University of New York. Exclusion criteria for participation included HIV infection, maternal psychosis, maternal age <15 years, life-threatening maternal medical

complications, and congenital or chromosomal abnormalities in the fetus. Further details of the study can be found elsewhere (Finik, & Nomura, 2017).

Measures

Prenatal Exposure to Superstorm Sandy—Exposure status was defined according to whether mothers were pregnant at the time when SS made landfall or not pregnant during SS. Severity of stress caused by SS (objective and subjective) was measured and accounted for in the analytic approach (see below).

Child psychopathology—We collected diagnostic data for preschool children ages 2–5 using the PAPA (Egger, Erkanli, Keeler, Potts, Walter, et al., 2006), a Parent-Report-only interviewer-based structured diagnostic interview for use with preschoolers (validated for ages 2–5). Most sections of the PAPA include some behaviors regarded as being normal in preschoolers at certain levels of frequency, and pathological at other levels (e.g., temper tantrums, impulsivity). The PAPA also excludes developmentally inappropriate items (e.g., sexual activity, substance use, and certain conduct problems such as truancy or car stealing). The PAPA assesses four categories of DSM-IV diagnoses which are prevalent in young children - *anxiety disorders* [separation anxiety disorder (SAD), selective mutism, generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD)], *phobias* (simple, specific, and social), *depressive disorders* [major depressive disorder (MDD), dysthymia, and depressive disorders not otherwise specified (DDNOS), and *attention deficit and disruptive behavioral* disorders [attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), oppositional defiant disorder (ODD)]. When a positive diagnosis is suspected based on gatekeeping questions for each diagnostic category, the interviewers explore symptoms in depth, and record frequency, duration, and age of first onset, within a 3-month window, as well as lifetime occurrence and diagnosis. We assessed all disorders in each of the four categories examined regardless of whether there was a positive probe.

Interrater reliabilities during our training were fair to very good [specific phobia (k =.46), social phobia (k =.54), GAD (k =.59), separation anxiety disorder (k =.60), ODD (k =.62), CD (k =.66), dysthymia (k =.72), ADHD (k =.78), and selective mutism (k =.88)].

Potential Confounders—We examined 11 potential confounders, including 7 demographic variables, 2 SS-related stress (objective and subjective) levels, 1 factor for prenatal maternal substance use, and 2 concurrent psychosocial factors within the family.

Child and maternal demographic variables.: Demographic confounders included race, ethnicity, maternal age, parity, and marital status. Note that child sex was not included as a confounder, because sex differences in risks were examined separately.

Socioeconomic Status (SES).: Latent Class Analysis (Evans, & Mills, 1998) was used to extract SES using four demographic indicators: maternal education, pre-pregnancy occupation prestige, work status, and welfare status (Nomura, et al., 2021). Three SES categories were extracted: low (35.0%), medium (42.3%), and high (22.7%).

Objective and subjective stress due to SS.: Objective stress was assessed by the Storm32 scale (King & Laplante, 2005). The Storm32 has 20 questions that encompass salient aspects of disaster exposure within 30 days after the disaster. Examples include: did your residence suffer damage as a result of Hurricane Sandy; did you experience a loss of personal income; did your family stay together for the duration of the storm; were you in danger as a result of downed electrical power lines; did you experience lack of potable water? Mean (SD) was 2.90 (2.98); range was 17; internal consistency was α=.90. Subjective stress was measured by mother's posttraumatic stress symptoms related to SS experiences, using the Impact of Events Scale-Revised (IES-R), (Weiss, & Marmar, 1997). This scale was modified to specifically ask about SS-related trauma. Internal consistency for the IES-R was α=.91.

Normative prenatal stress: Normative prenatal stress was extracted using latent profile analysis (LPA, Tein, Coxe, & Cham, 2013) with the Pregnancy-related anxiety questionnaire-revised (PRAQ-R). Mother's depression symptoms were measured by the Edinburgh Postnatal Depression Scale (EPDS)(Murray, & Carothers, 1990); anxiety symptoms were measured by the State- and Trait- Anxiety Inventory (STAI) (Spielberger, 1989), the 14-item Perceived Stress Scale (PSS-14) (Cohen, 1988), and Life Events. Internal consistency for the PRAQ-R, EPDS, and STAI, and PSS-14 were α=.86, α=.84, α=.89, and α=.91, respectively. LPA tested 2- and 3-class solutions, which both showed good model fit with entropy of 0.8 or greater and significant Lo-Mendell-Rubin (L-M-R) test scores. Both the BIC and ABIC values decreased from the 2-class model to the 3-class model. When comparing the model fits between 2-class and 3-class models, there was a significant improvement (p=.0021). The details can be found in Table S1. Taken together, the 3-class model (low, medium, and high) was selected.

Concurrent psychosocial factors (maternal affection and family stress) at age 3.: Maternal affection was assessed using the parental bonding instrument (Parker et al., 1979), which asks about fundamental dimensions of maternal affection and control. The internal consistency for affection items was α=.90. Family Stress was measured by the Parenting Stress Index Short-form (Abidin, 2012), which asks about problems with the child's or parent's behavior within the family unit, covering defensive responses, difficult child behavior, parental distress, and parent–child dysfunctional Interaction. The internal consistency was α = .89.

Mother's substance use.: The absence or presence of tobacco, cannabis, alcohol, and cocaine use were ascertained by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, & Gibbon, 2004) with expecting mothers during pregnancy.

Statistical method

Prior to the main analyses, demographic differences between the two SS groups were examined using analysis of variance for continuous variables, and chi-square tests for categorical variables.

To evaluate differences in onset, log-rank test was used in survival analysis techniques by means of a modified Kaplan-Meier method (Williams, 1995) in the two SS groups, and then

in four groups - defined by SS exposure and child sex. Cox proportional hazards regression models (Cox, 1972) estimated the cumulative risks of each disorder in the exposed relative to the unexposed. Hazard ratio (HR) was calculated as an index of cumulative risks. Both unadjusted and adjusted models with covariates were tested. Adjusted model 1 included SS exposure status and all but two concurrent psychosocial confounders, and adjusted model 2 had the two additional concurrent measures in childhood as covariates. The same set of analyses was repeated after stratifying on child sex.

The adjustment for clustered data was necessary to account for potential nonindependence of outcomes from the same family (n=12 siblings). To overcome the potential violation of the assumption of independence of the outcomes, we used the methods of Binder (Binder, 1982) to remove the cluster effects from the results.

Results

Demographic characteristics

The study population is diverse, including Black (19.0%), Asian (9.2%), and mixed race (30.7%). The majority are Hispanic (57.7%). Notably, 85.5% are from a racial or ethnic minority group, including financial minority - with 35% being from low SES, and 42.3% from medium SES. As can be seen in Table 1, there were no major demographic differences between the two SS groups.

Developmental disorders in male and female children by SS exposure

The top panel in Figure 2 demonstrates the patterns of onset over time for anxiety disorders, attention deficit/disruptive behavioral disorders, and any of the disorders we examined in relation to exposure to SS *in-utero*. Solid lines represent exposed [SS(+)] and dotted lines unexposed [SS(−)]. The bottom panel in Figure 2 shows sex-specific age of onset. Red lines represent female, and blue lines male children. Panels A, B, and C show the Kaplan-Meier (survival) curves for anxiety disorders, attention deficit/disruptive behavioral disorders, and any disorder in the four strata respectively.

The test of equality of strata among the four groups by SS exposure and sex shows significant differences in the patterns of onset over time for anxiety disorders ($\chi^2(3)=23.96$, $p<.0001$) and attention deficit/disruptive behavioral disorders ($\chi^2(3)=21.18$, $p<.0001$), but not any disorder ($\chi^2(3)=5.86$, $p=.11$). Further stratification analysis by child sex showed that the survival curves by SS exposure were significantly different for attention deficit/disruptive behavioral disorders ($\chi^2(1)=11.71$, $p=.001$) only in males, whereas there were significant differences in anxiety disorders ($\chi^2(1)=16.91$, $p<.0001$) and any disorder ($\chi^2(1)=5.58$, $p=.02$) only in females. Table S2 shows the different survival distributions with all subcategories of disorders.

Risk of psychiatric disorders in children by SS exposure *in-utero*

In Table 2, the second column shows the rate of disorders in the two groups (exposed/unexposed) in 4 diagnostic categories. Rates were high in both groups but especially elevated in those exposed to SS. Exposed children had a higher rate of anxiety disorders

(53.0%/21.6%), as well as subcategories including SAD (43.9%/18.6%) and GAD (19.7%/2.1%). Exposed children also had higher rates of dysthymia (9.1%/1.0%) but there were no cases of MDD or DDNOS. Exposed children had higher rates of attention deficit/disruptive behavioral disorders (30.3%/8.2%), as well as subcategories including ADHD (18.2% / 4.1%), CD (15.2%/3.1%), and ODD (19.7%/6.2%). Any disorder was higher in exposed children (69.2%/51.0%).

The third and fourth columns of Table 2 shows the magnitude of unadjusted (HR) and adjusted risks (HR) with 95%CI respectively. *In-utero*-exposed children had a 5-fold increased risk for anxiety disorders (HR=5.05, 95%CI=2.51–10.18, $p<.0001$) as well as a 3-fold increased risk for SAD (HR=3.51, 95% CI=1.65–7.46, $p=.001$) and an 8-fold increased risk for GAD (HR=8.51., 95% CI=1.98–36.54, $p=.004$). For depression, there was a greater than 16-fold increased risk for dysthymia (HR=16.87, 95%CI=1.41–201.91, $p=.03$). Exposed children had an over 3-fold increased risk for attention deficit/disruptive behavioral disorders (HR=3.36, 95%CI=1.24–9.13, $p=.02$, as well as an over 5-fold increased risk for ADHD (HR=5.46, 95%CI=1.46–20.49, $p=.01$), a 4-fold marginally increased risk for CD (HR=4.86, 95%CI=0.82–28.77, $p=.08$), and an almost 4-fold increased risk for ODD (HR=3.75, 95%CI=1.07–2.99, $p=.03$) in the subcategories of attention deficit/disruptive behavioral disorders. Lastly, there was an almost 2-fold increased risk for any disorder (HR=1.79, 95%CI=1.07–2.99, $p=.03$).

Risk of psychiatric disorders from SS exposure *in-utero* in female and male children

Table 3 shows the sex-specific risk of disorders among children exposed relative to unexposed to SS. The risk for anxiety disorders (HR=10.03, 95%CI=3.25–30.95, $p<.0001$), and phobia (HR=2.76, 95%CI=1.18–6.44, $p=.02$) by SS exposure was substantially elevated only in females, but not in males. Specifically, SS exposure was associated with a 9-fold increased risk for SAD (HR=9.48, 95%CI=3.06–29.38, $p<.0001$) and an almost 20-fold increased risk for GAD (HR=20.11, 95%CI=2.17–186.39, $p=.008$). Among males, however, associations were not significant, nor was the magnitude as notable as in females. In contrast, there were substantial increased risks seen in the attention deficit/disruptive behavioral disorders category in males (HR=7.82, 95%CI=1.38–44.39, $p=.02$), but not in females. SS exposure was associated with a 62-fold increased risk for ADHD (HR=62.81, 95%CI=1.24–4267.90, $p=.04$), a 20-fold increased risk for CD (HR=20.40, 95%CI=1.06–362.41, $p=.05$), and a 15-fold increased risk for ODD (HR=15.29, 95%CI=1.48–157.54, $p=.02$) in males. Among females, however, associations were not significant, nor was the magnitude as notable as in males. Lastly, there was an over 3-fold increased risk for any disorder (HR=3.05, 95%CI=1.46–6.37, $p=.003$) among females, but not males.

Discussion

This study has two major findings. First, exposure to SS *in-utero* was associated with a substantial increase in risk for anxiety disorders, depressive disorders, and attention deficit/disruptive behavioral disorders. Second, exposed males had a substantially elevated risk for attention deficit/disruptive behavioral disorders, including ADHD, CD, and ODD, compared

to females, whereas females had a substantially elevated risk for anxiety disorders, phobia, and depressive disorders, including SAD, GAD, specific phobia, and dysthymia.

In recent years, there has been an increasing occurrence of major natural disasters. Systematic longitudinal follow-up with structured interviews allowed us to examine the degree to which exposure to SS *in-utero* was associated with the development of specific psychiatric disorders instead of atypical, but not fully categorized behavioral symptoms, in exposed relative to unexposed offspring. To our knowledge, this is the first study to demonstrate increased risk for emerging psychopathology in a sex-specific manner among preschool-aged children exposed to SS *in-utero*.

Our findings are extremely alarming. The data showed an over 5-fold increased risk for anxiety disorders, an over 16-fold increase in depression, and an over 3-fold increased risk for attention deficit/disruptive behavioral disorders. Patterns of onset of disorders are consistent with prior findings (Ping et al., 2015; Vernberg, et al., 1996) which demonstrated that exposure to prenatal stress is related to an increase in anxiety in females, but not males. The current findings provide further evidence that the age of onset of attention deficit/disruptive behavioral disorders is earlier, and the magnitude of risks is much greater among male children than females following exposure to prenatal stress. Elevated risks for individual disorders are also noteworthy. SS exposure *in-utero* was associated with a substantial increase in SAD (HR=9.5), GAD (HR=20.1), dysthymia (HR=30.0), and specific phobia (HR=2.5) in females, while substantial increases in males were observed for ADHD (HR=62.8), CD (HR=20.4), and ODD (HR=15.3).

While it is clear that exposure to natural disasters poses significant risks to pregnant women and their offspring *in-utero*, the mechanism through which this occurs remains unknown. Recently, we examined how underlying biological mechanisms that link prenatal exposure to SS and child outcomes coincide with the reorganization of placental transcriptome via vascular, immune, and endocrine gene pathways (Nomura, Rompala, Prichett, Aushev. et al., 2021). It is possible for changes in placenta transcriptomes to set the trajectories of clinical and neurobehavioral development in exposed children via cascades of changes in those systems, which all have important functions in modulating psychosocial stress. It is also possible that the exposure to a natural disaster during pregnancy continued to negatively shape the family functioning and distress after birth of the child (Schleider et al., 2015), and that in turn influenced the age of onset of developmental psychopathology in pre-school children. To help remove such possible mechanisms, we added two important concurrent factors in childhood to our analytical models – maternal warmth and family stress - that shape important aspects of family environment during early childhood. We found that the family environment in childhood uniquely influenced the elevated risks for specific phobia and ADHD in males, but prenatal disaster-related stress remained a significant risk for anxiety and depressive disorders, and phobia in females and attention deficit/DBD disorders in males. It is, of course, possible that prenatal and concurrent stress could synergistically elevate the risk for psychopathology. While that is beyond the scope of the current study, future analyses will attempt to address this question.

It is also important to consider findings from recent neuroimaging studies on sex differences in the developing brain – which highlight differences in how male and female brains develop. There has been considerable interest in developmental structural sex differences in the medial temporal lobe (amygdala and hippocampus). To date findings are mixed (Ruigrok, Salimi-Khorshidi, Lai, Baron-Cohen, Lombardo, et al., 2014), with some pointing to larger structures in males (Suzuki, Hagino, Nohara, Zhou, Kawasaki, et al., 2005), others to larger structures in females (Giedd, Blumenthal, Jeffries, Castellanos, Liu, et al., 1999), and yet others finding no significant difference (Marwha, Halari, & Elliot, 2017). More specifically, some studies have reported that prenatal stress is associated with smaller volume in the left and right hippocampus in males, (Buss, Davis, Shahbaba, Pruessner, Head, et al., 2012) with an increase in the volume in right amygdala being associated with increased externalizing problems in males (Jones, Dufoix, Laplante, Elgbeili, Patel, et al., 2019). One notable finding is that fronto-limbic connectivity in association with prenatal stress is stronger in females than in males (Wheelock, Hect, Hernandez-Andrade, Hassan, Romero, et al., 2019; Graham, Rasmussen, Entringer, Ward, Rudolph, et al., 2019). Differences in connectivity between the two sexes offers a possible explanation for the sex dimorphism findings for risk of psychopathology. Furthermore, prenatal stress is associated with larger right amygdala volume in female children, but not male, which in turn is associated with increased affective and internalizing problems; however, there is still disagreement as to whether and how the timing of exposure in gestation that can influence this association (Buss et al., 2012; Jones et al., 2019).

Our study has several strengths. First, unlike most studies, where prenatal stress has been largely addressed as a reflection of normative stress in everyday life, (Rubonis, & Bickman, 1991) as maternal psychopathology, or as a result of low SES, our study examined the effects of a large-scale disaster firsthand (Braithwaite et al., 2017; Huizink, Dick, Sihvola, Pulkkinen, Rose, 2007; Laplante, et al., 2016; Nomura, Davey, Pehme, Finik, Glover, et al., 2019; Yehuda, Engel, Brand, Seckl, Marcus, et al., 2005). SS offered a rare opportunity to apply a quasi-experimental design to study the impact of exposure to weather-related disaster. Given the projected increase in the frequency of natural disasters, these data provide timely and useful information on the potential consequences of disaster exposure *in-utero* on developmental psychopathology. Second, use of a structured interview, the PAPA, designed to assess DSM-IV disorders in preschool aged children, provided excellent support for our estimates of increased risks of developmental psychopathology for high-risk children. Examining diagnostic outcomes enabled us to more specifically describe the nature and magnitude of risk as a function of exposure to SS. Third, the study uncovered sex-specific increased risks in different types of disorders. Specifically, it documented greater risks for attention deficit/disruptive behavioral disorders in male children and anxiety disorders in females.

The study also has limitations. First, it is based on a subsample of children (all preschool aged children) from a larger longitudinal study. However, there were no notable differences in the pertinent demographics and stress variables between the preschool aged children who participated in this diagnostic study (n=163), which was implemented after the longitudinal study began, and the older population (n=195) in the larger study pool (Table S3). Second, the clinical interviews were based solely on maternal report. While maternal report is the

gold standard for assessing psychopathology in preschool children, there is potential for bias as a function of maternal psychopathology or maternal reaction to the disaster. To better isolate the contribution of environmental stressors to the outcomes we reported, our analytic model controlled for maternal posttraumatic stress symptoms and objective challenges due to SS exposure, as well as maternal anxiety and depressive symptomatology. Of note, SS unexposed mothers had higher depression ratings than those who were SS exposed, so maternal depression does not account for the higher diagnostic rates in SS exposed offspring. Third, the study does not have measures of two concurrent psychosocial measures (maternal warmth and family stress) in the early period after birth (i.e., first 6 months of life) to assess potential confounding effects of this developmentally important period of a child's life. However, we incorporated the measures we assessed when the child was age 3 in the adjusted model when estimating the risks. Forth, inter-rater reliability for the childhood disorders we studied could have been better. However, the reliability rates reported for the PAPA are similar to those for older children reported elsewhere (Egger, Erkanli, Keeler, Potts, Walter, et al., 2006). Fifth, while it is possible that the small sample size in this study might have inflated the risk estimates, it is important to note that we have used survival analysis to examine the cumulative risk over time (i.e., HR). HRs provide more accurate and robust estimates than odds ratios when estimates are based on a small sample size. Nevertheless, readers should interpret the sex-specific magnitude of risks, especially for ADHD, CD, and ODD, with caution. Sixth, the prevalence of some diagnoses, including selective mutism, PTSD, and depressive disorders, was very low. This was to be expected, given the age of the population. Seventh, gestational age at the time of disaster exposure could differentially influence the magnitude of risks. However, as our sample also included children who were unexposed to SS *in-utero* in a control group, gestational age was not adjusted for in the study. Finally, we were not able to evaluate the level of environmental toxins and air quality that the SS exposed mothers might have encountered — one of no doubt many associated factors that could have also influenced the associations between the *in-utero* hurricane exposure to the child outcomes.

The current study demonstrates associations between *in-utero* exposure to a major climate disaster and early development of psychiatric disorders, and provides initial evidence of distinct psychopathological outcomes as a function of sex. We acknowledge that these results are based on a relatively small sample size and need to be replicated in future studies. However, we report them here because of the magnitude of the findings, the uniqueness of this study, and the recognition that there may not be another opportunity to conduct a study such as this one for some time. Unfortunately, given the enormity of the direct and indirect consequences of SS, our attention and resources as a society have not been allocated to monitoring and charting the developmental consequences of SS among those exposed to the events *in-utero* — one of the most critical developmental periods for children. It is essential that women in reproductive ages and their families be informed about the potential long-term consequences for their offspring when exposed to disaster-related stressors during pregnancy. As the intensity and frequency of weather-related disasters are forecasted to increase, it is critical to understand the long-term consequences for mental health on children exposed to these disasters *in-utero* and to examine sex-specific effects on this exposure. It is helpful for policy makers, obstetricians, and pediatricians to create an

infrastructure to assist pregnant women and their families when confronting such a natural disaster, to mitigate risks to their children *in-utero*, support healthy development after birth, and prevent psychiatric disorders. Finally, it is important to adapt longitudinal studies such as this one to evaluate the long-term influences of natural disasters, when they occur, on the mental health outcomes of infants and young children in the years ahead.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SS	Superstorm Sandy
PAPA	the preschool age psychiatric assessment
HR	hazard ratio
aHR	adjusted hazard ratio
ADHD	attention-deficit/hyperactivity disorder
CD	conduct disorder
ODD	oppositional defiant disorder
SAD	separation anxiety disorder
GAD	generalized anxiety disorder

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Key points

- Prenatal stress, in the form of a natural disaster, increased the risk for preschool children's psychopathology, especially anxiety, depressive, and attention deficit/disruptive behavior disorders. Male children had a substantially greater risk for attention deficit/disruptive behavior disorders, whereas females had greater risk for anxiety disorders.
- Emerging psychopathology following exposure to a natural disaster *in utero* can be identified as early as the preschool years.
- It is presumed that this increased risk for psychiatric disorders is mediated through a variety of parent, child and environmental factors, including possible gene × environment interactions. Further research is required to elucidate these mechanisms.
- The frequency of natural disasters is increasing. Parents, educators and pediatricians should be aware that young children exposed to such events are at increased risk for the development of psychiatric disorders – even when those events occur *in utero* – and monitor for the possible emergence of psychiatric disorders.
- Policy makers, obstetricians, and pediatricians need to create an infrastructure to assist pregnant women and their families when confronting a natural disaster, to mitigate risks to their children *in-utero*, support healthy development after birth, and reduce subsequent psychiatric disorders.

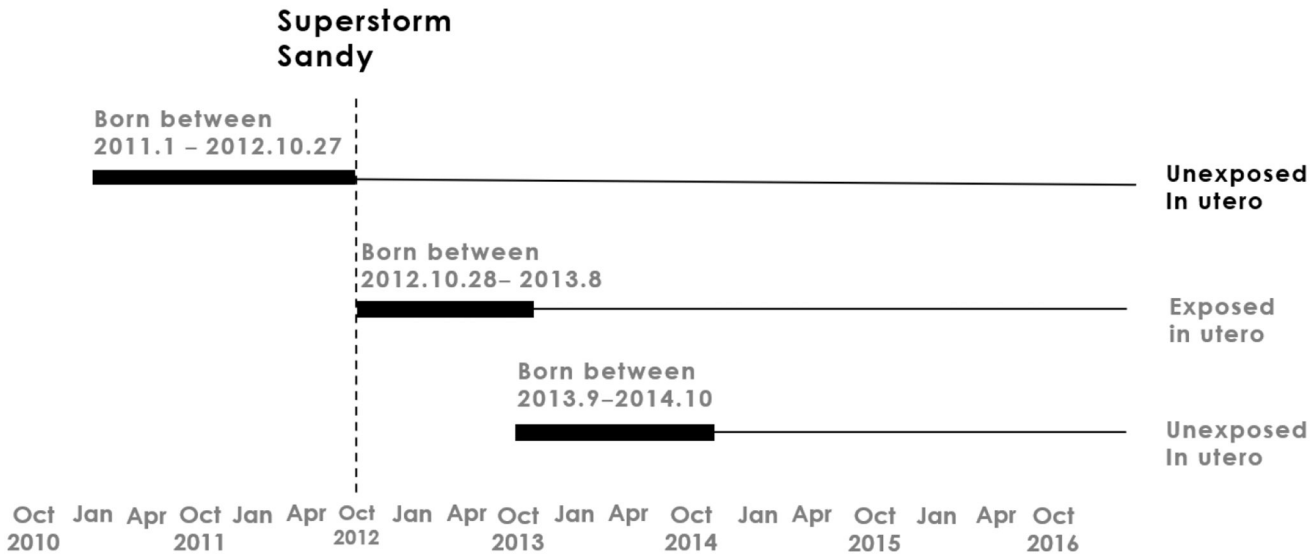

Figure 1.
SIP Study – Exposure to Superstorm Sandy *in utero*

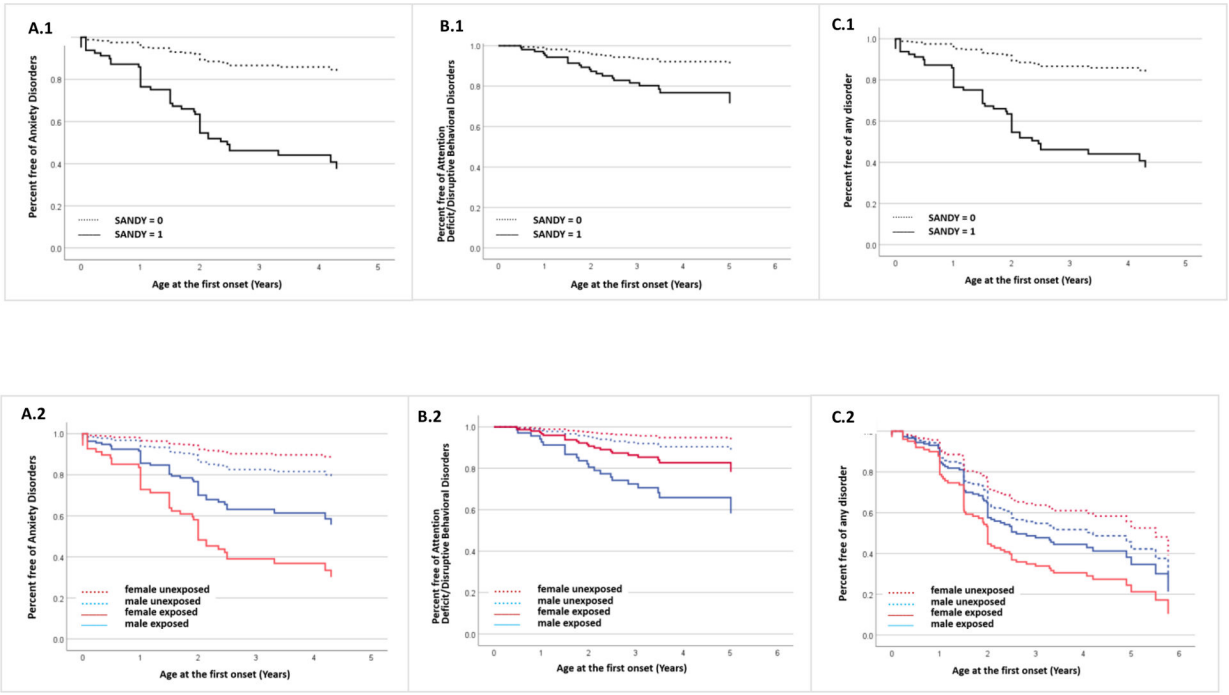

Figure 2.

The test of equality on survival distributions by Superstorm Sandy exposure status for anxiety disorders, disruptive behavioral disorders, and any disorder by Superstorm Sandy exposure (A.1, B.1, C.1) and by Superstorm Sandy exposure and child sex (A.2, B.2, C.2).

Legends for A.1., B.1, and C.1:

A. Anxiety disorders (X^2=16.95, df=1, p<.0001); B. Disruptive behavioral disorders (X^2=12.13, df=1, p=.0005); and C. any disorder (X^2=4.60, df=1, p=.03).

Legends for A.2., B.2., and C.2:

Boys: A. anxiety disorders (X^2=1.37, df=1, p=.24), B. disruptive behavioral disorders (X^2=11.71, df=1, p=.001), and C. any disorder (X^2=0.45, df=1, p=.50). Girls: A. anxiety disorders (X^2=16.91, df=1, p<.0001), B. disruptive behavioral disorders (X^2=2.61, df=1, p=.11), and C. any disorder (X^2=5.58, df=1, p=.02).

Panel A for anxiety disorders, panel B for disruptive behavioral disorders, and panel C for any disorder.

Solid lines represent exposed [SS(+)] and dotted lines unexposed [SS(−)]. Red lines represent girls and blue lines boys.

Anxiety disorders include separation anxiety, generalized anxiety disorder, selective mutism, and posttraumatic stress disorder. Disruptive behavioral disorders include conduct disorder, oppositional defiant disorder, and attention deficit hyperactivity disorder. Any disorder includes any of the above disorder.

Results for single disorders that are a part of anxiety disorders (separation anxiety disorder, generalized anxiety disorder, selective mutism) and disruptive disorders (conduct disorder, oppositional defiant disorder, and attention deficit/hyperactivity disorder) can be found in Table S2.

Table 1.

Demographic characteristics of the sample by exposure to Superstorm Sandy

	Total Sample (n=163)	Unexposed (n =97)	Exposed (n = 66)	Statistics
Child Race, N (%)				
White	67 (41.1)	35 (36.1)	32 (48.5)	
Black	31 (19.0)	23 (23.7)	8 (12.1)	
Asian	15 (9.2)	11 (11.3)	4 (6.1)	
Mixed/Others	50 (30.7)	28 (28.9)	22 (33.3)	$X^2(3)=5.69$, $p=.13$
Child Ethnicity, N (%)				
Hispanic	94 (57.7)	46 (47.4)	23 (34.8)	
Non-Hispanic	69 (42.3)	51 (52.6)	43 (65.2)	$X^2(1)=2.54$, $p=.11$
Child Sex, N (%)				
Girls	87 (53.4)	47 (48.5)	40 (60.6)	
Boys	76 (46.6)	50 (51.5)	26 (39.4)	$X^2(1)=2.33$, $p=.13$
Parity, Mean (SD)	2.08 (1.60)	1.98 (1.61)	2.23 (1.59)	$F(1,161)=0.98$, $p=.33$
Marital Status, N (%)				
Married	79 (48.5)	38 (54.3)	28 (52.8)	
Common Law Marriage	8 (4.9)	3 (4.3)	2 (3.8)	
Single	70 (42.9)	28 (40.0)	19 (35.8)	
Separated/Divorced	6 (3.7)	1 (1.4)	4 (7.5)	$X^2(9)=13.0$, $p=.16$
Maternal Age, Mean (SD)	27.80 (5.92)	27.63 (5.98)	28.05 (5.87)	$F(1,161)=.19$. $p=.66$
Paternal Age[a], Mean (SD)	30.37 (6.94)	30.34 (7.02)	30.40 (6.85)	$F(1,156)=.003$, $p=.96$
Socioeconomic Status (SES), N (%)				
High	37 (22.7)	20 (20.6)	17 (25.9)	
Medium	69 (42.3)	43 (44.3)	26 (39.4)	
Low	57 (35.0)	34 (35.1)	23 (34.8)	$X^2(6)=0.68$, $p = .71$
Normative prenatal stress, N (%)				
High	58 (34.4)	32 (33.0)	24 (38.4)	
Medium	79 (48.5)	47 (48.4)	32 (48.5)	
Low	28 (17.2)	18 (18.6)	10 (15.2)	$X^2(2)=.40$, $p=.82$
Objective Sandy stress, Mean (SD)	2.86 (2.64)	2.53 (2.38)	3.34 (2.95)	$F(1, 161)=3.59$, $p=.06$
Posttraumatic stress[b], Mean (SD)	7.34 (12.21)	7.45 (13.12)	7.18 (9.12)	$F(1, 161)=0.02$, $p=.88$
Yes, N (%)	13 (8.0)	8 (9.3)	4 (6.1)	
No, N (%)	150 (92.0)	88 (90.7)	62 (93.9)	$X^2(1)=.55$, $p=.46$
Prenatal depression[c], Mean (SD)	9.40 (5.01)	10.01 (5.18)	8.52 (4.66)	$F(1.151)=3.55$, $p=.11$
Yes, N (%)	68 (44.4)	46 (48.9)	22 (37.3)	
No, N (%)	85 (55.6)	48 (51.1)	37 (62.7)	$X^2(1)=1.99$, $p=.16$
Prenatal anxiety[d], Mean (SD)	77.92 (20.41)	78.76 (21.18)	76.67 (19.34)	$F(1,151)=.35$, $p=.46$
Yes, N (%)	65 (42.8)	42 (44.7)	24 (40.7)	

	Total Sample (n=163)	Unexposed (n =97)	Exposed (n = 66)	Statistics
No, N (%)	87 (57.2)	52 (55.3)	35 (59.3)	$X^2(1)=.24$, $p=.63$
Prenatal substance use, N (%)				
Yes	24 (14.7)	14 (14.4)	10 (15.3)	
No	139 (85.3)	83 (85.6)	56 (84.8)	$X^2(1)=.02$, $p=.90$
Time of exposure (exposed group)				
Third trimester	34 (51.4%)		34 (51.4%)	
Second trimester	19 (28.8%)		19 (28.8%)	
First trimester	13 (19.7%)		13 (19.7%)	--
Time of exposure (control group)				
Post-SS	41 (42.3%)	41 (42.3%)		
Pre-SS	56 (57.7%)	56 (57.7%)		--

[a] There are 5 cases with missing values.

[b] Measured by **t**he Impact of Events Scale-Revised (IES-R) specific to Sandy. The cut-off point of 22 was used for positive and negative PTSD.

[c] Measured by Edinburgh Postnatal Depression Scale (EPDS); there are 10 cases with missing value. The cut-off point of 10 was used for positive and negative depression.

[d] Measured by State-Trait Anxiety Inventory (STAI). A total score (State Anxiety and Trait Anxiety) was used. The cut-off point for the total score of 82 (41 for State and 41 for Trait) was used for positive and negative anxiety. There are 10 cases with missing values.

Table 2.

Risks of Psychiatric Disorders[a] in Preschool-aged Children who werf Exposed and Unexposed to Superstorm Sandy *in-utero* (N=163)

	***in utero* SS exposure**							
	Unexposed	**Exposed**						
	(n=97)	**(n=66)**	**Unadjusted model**		**Adjusted model 1[e]**		**Adjusted model 2[f]**	
	N (%)	**N (%)**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
any Anxiety Disorders [b]	21 (21.6)	35 (53.0)	**2.93 (1.70–5.45)**	**<.0001**	**3.80 (2.08–6.96)**	**<.0001**	**5.05 (2.51–10.18)**	**<.0001**
Separation anxiety (SAD)	18 (18.6)	29 (43.9)	**2.53 (1.40–4.56)**	**.002**	**2.90 (1.52–5.54)**	**.001**	**3.51 (1.65–7.46)**	**.001**
Generalized Anxiety Disorder (GAD)	2 (2.1)	13 (19.7)	**7.00 (1.99–24.57)**	**.002**	**7.65 (2.01–29.06)**	**.003**	**8.51 (1.98–36.54)**	**.004**
Selective mutism	2 (2.1)	3 (4.5)	2.28 (0.38–13.66)	.37	NE[d]		NE[d]	
Post-traumatic stress disorder (PTSD)	0	2 (3.0)	NE	.52[c]	NE[d]		NE[d]	
any Phobia [b]	41 (42.3)	31 (47.0)	1.13 (0.71–1.81)	.60	1.27 (0.75–2.15)	.37	1.34 (0.76–2.34)	.32
Social phobia	11 (11.3)	13 (19.7)	2.14 (0.79–5.81)	.14	2.12 (0.84–5.38)	.11	2.22 (0.82–6.03)	.12
Specific phobia	38 (39.2)	26 (39.4)	1.01 (0.61–1.66)	.97	1.31 (0.75–2.27)	.35	1.36 (0.71–2.59)	.35
Agora phobia	2 (2.1)	0	NE	.52[c]	NE[d]		NE[d]	
any Depressive Disorders	1 (1.0)	6 (9.1)	**9.09 (1.09–75.47)**	**.04**	**12.24 (1.27–118.35)**	**.03**	**16.87 (1.41–201.91)**	**.03**
Major Depressive Disorder (MDD)	0	0	--		--			
Dysthymia	1 (1.0)	6 (9.1)	**9.09 (1.09–75.47)**	**.04**	**12.24 (1.27–118.35)**	**.03**	**16.87 (1.41–201.91)**	**.03**
Depressive Disorder NOS (DDNOS)	0	0	--		--		--	
any Attention Deficit/DBDs	8 (8.2)	20 (30.3)	**4.13 (1.82–9.39)**	**.001**	**4.59 (1.80–11.68)**	**.001**	**3.36 (1.24–9.13)**	**.02**
Attention Deficit/Hyperactivity Disorder (ADHD)	4 (4.1)	12 (18.2)	**4.58 (1.47–14.24)**	**.009**	**6.81 (1.87–24.73)**	**.004**	**5.46 (1.46–20.49)**	**.01**
Conduct Disorder (CD)	3 (3.1)	10 (15.2)	**5.17 (1.42–18.81)**	**.01**	**10.22 (1.85–56.43)**	**.008**	4.86 (0.82–28.77)	.08
Oppositional Defiant Disorder (ODD)	6 (6.2)	13 (19.7)	**3.51 (1.33–9.23)**	**.01**	**5.48 (1.70–17.66)**	**.004**	**3.75 (1.02–13.80)**	**.05**
any Disorders	50 (51.0)	45 (69.2)	**1.53 (1.02–2.28)**	**.04**	**1.58 (1.01–2.47)**	**.05**	**1.79 (1.07–2.99)**	**.03**

[a]Diagnoses are at the definite level, with impairment defined as a score less than 70 on the Global Assessment Scale.

[b]Anxiety disorders do not include phobia and phobia does not include anxiety disorders

[c]P-value is based on two-tailed Fisher exact test.

[d]Number of cases was not sufficient to estimate HRs nor conduct multivariate analysis.

[e] Adjusted model 1 includes child race and ethnicity, maternal age, parity, marital status of the parents, SES, prenatal normative stress, prenatal substance use, posttraumatic stress symptoms-specific to SS, and objective Sandy stress as covariates.

[f] Adjusted model 2 includes child race and ethnicity, maternal age, parity, marital status of the parents, SES, prenatal normative stress, prenatal substance use, posttraumatic stress symptoms-specific to SS, objective Sandy stress, maternal affection and family stress at age 3 as covariates.

SS = Superstorm Sandy; HR = hazard ratio; CI = confidence interval; NOS = not otherwise specified; DBD = disruptive behavioral disorders.

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Table 3.

Sex difference in the cumulative risk of developmental psychopathology by exposure to Sandy *in-utero*

	Boys (n=76)						Girls (n=87)					
Outcomes	**Unadjusted model**		**Adjusted model 1**		**Adjusted model 2**		**Unadjusted model**		**Adjusted model 1**		**Adjusted model 2**	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Anxiety disorders	1.67 (074.−4.32)	.20	1..74 (0.54–5.57)	.35	1.57 (0.28–6.80)	.61	**4.10 (1.96–8.57)**	**.0002**	**5.693 (246–13.16)**	**<.0001**	**10.03 (3.25–30.95)**	**<.0001**
SAD	1.22 (0.46–3.27)	.69	0.94 (0.28–3.09)	.92	0.60 (0.10–3.66)	.58	**4.21 (1.86–9.52)**	**.0006**	**7.52 (2.67–21.17)**	**<.0001**	**9.48 (3.06–29.38)**	**<.0001**
GAD	8.62 (0.96–77.16)	.06	--		--		**6.54 (1.41–30.40)**	**.017**	**17.38 (2.09–144.61)**	**.008**	**20.11 (2.17–186.39)**	**.008**
Selective mutism	--		--		--		1.76 (0.29–10.51)	.54	1.19 (0.05–29.27)	.92	2.19 (0.23–20.67)	.50
Phobia	0.75 (0.35–1.62)	.47	0.79 (0.30–2.13)	.64	0.60 (0.17–2.10)	.44	**1.59 (0.85–2.97)**	**.15**	**1.76 (0.88–3.52)**	**.11**	**2.76 (1.18–6.44)**	**.02**
Social phobia	1.60 (0.36–7.16)	.54	1.39 (0.13–15.28)	.79	1.79 (0.21–15.56)	.60	1.83 (0.69–4.81)	.22	2.57 (0.78–8.43)	.12	2.63 (0.66–10.59)	.17
Specific phobia	0.66 (0.29–1.48)	.96	1.14 (0.41–3.15)	.80	1.03 (0.29–3.69)	.96	1.46 (0.72–2.81)	.30	1.58 (0.86–4.17)	.11	**2.54 (1.00–6.56)**	**.05**
Agora phobia	--		--		--		--		--		--	
Depressive disorders	NE		NE		NE		6.40 (0.75–54.78)	.09	23.11 (0.86–623.54)	.06	**30.02 (1.30–691.36)**	**.03**
MDD	--		--		--		--		--		--	
Dysthymia	NE		NE		NE		6.40 (0.75–54.78)	.09	6.60 (0.54–81.27)	.14	**30.02 (1.30–691.36)**	**.03**
DDNOS	--		--		--		--		--		--	
Attention deficit/ DBDs	**3.96 (1.46–10.75)**	**.007**	**9.11 (1.20–69.51)**	**.03**	**7.82 (1.38–44.39)**	**.02**	2.90 (0.75–11.20)	.12	4.94 (0.72–34.03)	.11	3.59 (0.66–19.58)	.14
ADHD	**4. 63 (0.89–24.20)**	**.07**	**86.46 (0.77–9754.16)**	**.06**	**62.81 (1.24–4267.90)**	**.04**	4.47 (0.93–21.54)	.06	5.20 (0.85–32.06)	.08	5.59 (0.71–60.92)	.10
CD	**15.61 (1.92–126.89)**	**.01**	**55.47 (2.94–1045.73)**	**.007**	**20.40 (1.06–392.41)**	**.05**	1.84 (0.31–11.03)	.50	2.79 (.30–26.30)	.37	1.99 (0.20–19.54)	.56
ODD	**5.98 (1.59–22.57)**	**.008**	**43.48 (2.97–635.99)**	**.006**	**15.29 (1.48–157.54)**	**.02**	2.14 (0.51–8.98)	.30	3.75 (0.70–20.17)	.12	3.11 (0.47–20.74)	.24
Any disorders	1.34 (0.45–3.47)	.60	1.58 (0.56–4.95)	.46	1.34 (0.45–3.47)	.60	**1.91 (1.10–3.32)**	**.02**	**3.15 (1.50–6.60)**	**.002**	**3.05 (1.46–6.37)**	**.003**

Adjusted model 1 includes child race and ethnicity, maternal age, parity, marital status of the parents, SES, prenatal normative stress, prenatal substance use, posttraumatic stress symptoms-specific to SS, and objective Sandy stress as covariates.

Adjusted model 2 includes child race and ethnicity, maternal age, parity, marital status of the parents, SES, prenatal normative stress, prenatal substance use, posttraumatic stress symptoms-specific to SS, objective Sandy stress, maternal affection and family stress at age 3 as covariates.

HR = hazard ratio; CI = confidence interval; NE = not estimable due to low prevalence; -- = no cases.

SAD = separation anxiety disorder; GAD = generalized anxiety disorder; MDD = major depressive disorder; DDNOS = depressive disorder not otherwise specified; DBD = disruptive behavioral disorder; CD = conduct disorder; ODD = oppositional defiant disorder; ADHD = attention deficit hyperactivity disorder.

Anxiety disorders includes SAD, GAD, SM, and PTSD. (PTSD is included as a part of anxiety disorders, but the prevalence was too low to be included in the sex-specific analysis.) Phobia includes specific phobia, social phobia, and agora phobia. Depression includes MDD, dysthymia, and DDNOS. Attention deficit/disruptive behavioral disorders (DBDs) include ADHD, CD, and ODD.